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MEMORANDUM

TO: PCCA

FROM: Hyman, Phelps & McNamara, P.C.

SUBJECT: Veterinary Compounding: An Overview of Why Applying the Compounding Quality Act to Veterinary Medicine Will Cripple Access to Needed Medications for the Treatment of Animals

I. Executive Summary

Veterinary drug compounding – the compounding of different drug products together or the creation of drug products from bulk chemical substances for administration to animals – is vital to the health, safety, and welfare of animals. **Because there are so few commercially manufactured prescription drugs available for the cure, treatment, and prevention of diseases in animals, especially animals that are not used in food production, veterinarians and the pharmacists who work with them have been safely compounding animal drugs for decades.**

The Drug Quality and Security Act ("DQSA") (enacted in late 2013) restructured federal law governing compounding for human drug preparations. The act removed unconstitutional provisions of Section 503A of the Federal Food, Drug, and Cosmetic Act ("FDCA") and created in Section 503B a new category of compounders – "Outsourcing Facilities." Outsourcing Facilities are explicitly authorized to compound sterile drugs for

office use,[1] but must adhere to standards generally applicable to commercial drug manufacturers including FDA's current good manufacturing practice ("cGMP"), 21 C.F.R. parts 201, 200. By contrast, Section 503A applies to more traditional compounding performed pursuant to a prescription for a specifically identified patient, and does not permit office use compounding in human health. Section 503A pharmacies traditionally have been regulated by State Boards of Pharmacy, and are typically held to standards set forth in USP <795> (Pharmaceutical Compounding - Nonsterile Preparations) and USP <797> (Pharmaceutical Compounding - Sterile Preparations).

The DQSA's statutory structure for human drug compounding would be wholly unworkable for veterinary compounding and jeopardize animal health. FDA policy already explicitly permits – with exceptions and restrictions – compounding pursuant to a written prescription for specifically identified animal patients, according to a guidance FDA issued in 2003.

Nevertheless, critical circumstances presented in veterinary health care ***require*** that compounding be permitted for patients that cannot be identified in advance; the essence of office use compounding. The requirements in Section 503B for office use compounding, however, would not be practical or effective for veterinary drugs. Furthermore, the requirements in Section 503A for compounding for individually

[1] **"Office use"** compounding is the compounding pursuant to an order that does not specify the identity of the patient, typically because the patient cannot be identified in advance. Office use compounding is critical for both human and animal health, particularly when the drug must be prepared and available for use in emergency situations, when the patient can otherwise not be practicably identified in advance, or if there would be increased risk to the patient if the drug could not be dispensed by the compounder until after the patient is identified. Recipients of drug products compounded for office use include veterinarians' or doctors' offices, hospitals, ambulances, and emergency clinics where the need for the drug can be predicted (leading to the order for the drug), but the identity of the patient will not be known until the treatment is required or the surgery is scheduled.

identified patients would unnecessarily complicate and confine veterinary drug compounding making it unworkable in practice, and threatening animal health.

II. Current Regulatory Environment

Between 2004 and 2014, there were multiple FDA seizures of compounded veterinary drugs or actions in which FDA successfully sought injunctions and consent decrees against veterinary compounders, although only one of those actions was recent.[2] FDA also has restricted imports of bulk drugs that could be used for compounding by veterinarians by imposing import detentions that do not require prior court approval. Other than discussed above, none of those cases led to relevant decisions by courts.

FDA has stated in repeated guidance documents and court filings that it considers office use compounding for animals and compounding from bulk chemicals for animals (with very limited exceptions) to be illegal, per se. But the only recent court decision examining the issue held that FDA's position is erroneous, and that compounding from bulk chemicals, at least for non-food-producing animals, is permitted under most circumstances.[3]

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[2] These actions included: A seizure warrant against BET Pharm. LLC, in Lexington, Kentucky in 2004; Warning Letters issued to Wickliffe Pharmaceuticals in Lexington, Kentucky in 2014 (eight horses died, severely subpotent (about 4 % of label claim) and superpotent (nearly 2,400 % of label claim) compounded drugs); BET Pharm. LLC (Nov. 17, 2003; commercial size lots, bulk chemicals; compounded drugs dispensed where health of animals not threatened); Grassland Veterinary Service (Sept. 30, 2003; use of prohibited chemicals in drugs compounded for lactating cattle); Lee Pharmacy (Oct. 6, 2003; use of bulk chemicals in veterinary compounding including camphorated oil and cisapride; copies of commercially available drugs); Medical Park Pharmacy (Nov. 25, 2003; use of bulk chemicals and cisapride); Kilgore Veterinary Associates (Aug. 7, 2003; no valid pharmacist-veterinarian-patient relationship, unsafe drugs); The Veterinary Pharmacy (Aug. 6, 2004; compounding using bulk chemicals, inadequate prescriptions); Veterinary Enterprises of Tomorrow (Dec. 8, 2004; compounding from bulk chemicals; office use compounding); *United States v. Franck's Lab.*, 816 F. Supp. 2d 1209 (M.D. Fla.), *vacated*, No. 11-15350, 2012 WL 10234948 (11th Cir. Oct. 18, 2012).

[3] *United States v. Franck's Lab.*, 816 F. Supp. 2d 1209.

III. The Human Drug Compounding Statutory and Regulatory Framework Won't Work for Animal Drugs.

A. "Office Use" of Veterinary Drugs is Critical for Animal Health.

- In veterinary health, an adequate supply of compounded medications for office use is essential for the proper care and treatment of animal patients.

- Veterinarians perform medical procedures – including emergency procedures for which a patient cannot be identified in advance – which necessitate keeping compounded medications in stock in order to perform those procedures.

- Veterinarians need to keep compounded office stock medications on trucks to take to their immobile or non-transportable patients, whether at a farm, stable, or zoo, for which they cannot identify patients in advance.

- Veterinarians compound medications from bulk substances, or use components of approved drugs, that are customized for various animals they routinely treat given the specialized and varied nature of their practice.

- Compounded medications for animals are highly specialized depending on breed, size, and other factors, and need to be available for immediate administration.

    - As one example, apomorphine is a drug that is used to treat poisoned animal patients; it is typically administered in a clinic to induce vomiting to rid the body of a poison. It must be available as an office supply stock in veterinary practices so that it is available when it is needed. Delaying for even an hour could cause the death of the animal; providing an individual prescription in advance is not feasible. There is no suitable commercially available apomorphine product for veterinary use.

B. Section 503B's Other Requirements for Compounding are Unworkable in the Animal Context.

- Registration, reporting and drug listing requirements under Section 503B would be impractical for veterinary compounding pharmacies.

- Section 503B's limitation to compounding medications from FDA's published shortage list and nothing else is unworkable in the animal drug context.

- Section 503B facilities may compound from bulk ingredients contained on a positive list developed by FDA for human health, but FDA has not yet developed that list, even though it has been nearly one year since passage of the law. This leaves industry uncertain as to which drugs can be compounded. Notably, FDA never finalized the positive list it attempted to promulgate in 1999 for human drugs under Section 503A. The bulk ingredients positive list is expected to be very short (as is the list of authorized bulk ingredients attached to the 2003 Guidance for veterinary drug products).

- Given the small markets for many veterinary medications, restricting compounding of animal drugs to a limited list of bulk substances or shortage medications affects treatment by limiting or eliminating effective compounded treatment options, and is detrimental to animal health.

- Almost 600 ingredients are used in animal drug compounding today. It is highly unlikely that any positive list like the ones (yet to be promulgated) for Section 503B and Section 503A compounders would be comprehensive enough to serve current needs, let alone future requirements.

- The requirement of inclusion on a positive list, and the likely process and time for FDA to include an ingredient on that list, would preclude any timely response to drug product discontinuations (which are not the same as shortages that appear on FDA's shortage list), which happen frequently with manufactured animal drugs.

- Veterinary compounders would not be able to compound on a scale sufficient to justify the cost of compliance with FDA's cGMP regulations (required of Section 503B facilities that are permitted to compound for office stock).

    - A recent FDA warning letter to a Section 503B facility shows that only high-volume compounding operations could possibly comply with cGMP requirements, including but not limited to stability testing requirements in FDA's Draft Guidance for Section 503B.

- While the volume, quantity, and pricing of many compounded human sterile drugs from FDA's drug shortage list may ensure sales necessary to compound and distribute those human drug preparations, many of the drugs produced by veterinary compounders likely would be sold by compounding pharmacies only in very small quantities. The quantities compounded by Section 503B facilities must be large enough to justify the high costs associated with compliance with cGMP requirements.

- Section 503B applies only to **sterile drugs compounded for office** use (although facilities may compound pursuant to prescriptions for individually identified patients). Section 503B is silent whether it applies to non-sterile drugs compounded for office use.

- Application of Section 503B cGMP requirements to non-sterile compounded animal drug preparations – especially for non-food-producing-animals - is impractical, and cost-prohibitive.

C. Section 503A Requiring Prescriptions for Individually Identified Patients is Unworkable for Veterinary Compounding.

- Veterinary medical practices often serve as emergency treatment centers where those practices are emergency rooms, pharmacies, and clinics; they rely on office use compounding; renders identification of patients impossible.

- Section 503A's still undefined interstate "5% state MOU" requirement for interstate compounding has no applicability for animal drug compounding. Compounding decisions must be made by availability and not state lines.

- Although, unlike Section 503B, Section 503A permits compounding from bulk substances with an approved USP/NF monograph, and pursuant to a "positive list," FDA has failed to publish a positive list of other substances that may be compounded under Section 503A.

D. *Especially with non-food-producing animals,* there is no human health threat caused by the compounding and dispensing of compounded veterinary drugs, which underscores how illogical it would be to impose a statutory scheme like Sections 503A and 503B of the FDCA on veterinary compounding.

E. Nearly 600 active ingredients are used in compounding for animal patients. Listed is a small sampling of animal drugs that simply cannot be produced without compounding, yet each is vital to animal health for many reasons:

- Acetylcysteine, used to treat acetaminophen and xylitol toxicity in cats and dogs.
- Ammonium Molybdate to treat copper poisoning in sheep.
- Calcium EDTA to treat lead poisoning in cats, dogs, rabbits, birds, small mammals, and horses.
- Methylene Blue to treat methemoglobinemia in dogs, cats, ruminants, and horses.
- Physostigmine to treat ivermectin toxicity in dogs, and tall larkspur poisoning in cattle.
- Sodium Thiosulfate used for arsenic and cyanide poisoning in dogs, cats, horses, and ruminants.
- Diethylstilbestrol used when indicated for incontinence in dogs and cats.
- Metronidazole Benzoate used to treat parasites in reptiles, amphibians, dogs, cats, birds, ferrets, rabbits, and small mammals.
- Cisapride used as a promotility agent used in cats, dogs, rabbits, rodents and small mammals.

F. A formulary for laboratory animals compiled in association with the American College of Laboratory Animal Medicine includes preparations for the treatment of animals; and ninety percent of these preparations must be compounded.

G. The Exotic Animal Formulary by James W. Carpenter, MS, DVM, Diplomate ACZM, covers fish, reptiles, birds, sugar gliders, hedgehogs, rodents, rabbits, ferrets, miniature pigs, and primates. Ninety eight percent of the preparations listed in the Formulary must be compounded.